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Original Article

Relationship of left atrial size to obstructive sleep apnea severity in end-stage renal disease

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ABSTRACT

Background: Increased left atrial (LA) size is linked to elevated mortality in end-stage renal disease (ESRD). In addition, the degree of overnight rostral fluid shift from the legs is associated with severity of obstructive sleep apnea (OSA). As rostral fluid shift might distend the left atrium and increase fluid accumulation in the neck, we postulated that LA size would be related to the degree of overnight rostral fluid shift and OSA severity in ESRD patients.

Methods: Patients with ESRD underwent echocardiography and polysomnography. Leg fluid volume (LFV) was measured by bioelectrical impedance before and after the overnight sleep study in a subset of 21 patients.

Results: Forty patients (22 men), with a mean apnea–hypopnea index (AHI) of 25.1 ± 23.4/h of sleep, had echocardiography and polysomnography performed. In men, there was a correlation between the AHI and LA size indexed for body surface area ($r = 0.743$, $p < 0.001$) that was not observed in women. Strong relationships were seen, again in men only, between LA size indexed to body surface area and the overnight change in leg fluid volume (ΔLFV) ($r = -0.739$, $p = 0.02$) and between AHI and ΔLFV ($r = -0.863$, $p = 0.003$).

Conclusions: In ESRD patients, there are relationships between ΔLFV and both LA size and OSA severity. These findings suggest that the relationship between LA size and mortality in ESRD may be related to ΔLFV and severity of OSA.

1. Introduction

Patients with end-stage renal disease (ESRD) have an annual mortality rate between 10% and 20%, mainly due to cardiovascular causes [1–3]. Increased left atrial (LA) size contributes to cardiovascular mortality in both the general population and in patients with ESRD [4,5]. In ESRD, the prevalence of obstructive sleep apnea (OSA), characterized by repetitive upper airway collapse during sleep, is at least 50% and is much higher than in the general population [6,7] with men having a higher prevalence than women [8]. In ESRD patients on peritoneal dialysis, the presence of OSA has been shown to be an independent predictor of cardiovascular morbidity and death [9]. It has also been shown that the severity of OSA is directly related to the degree of overnight fluid shift from the legs in ESRD [10]. Given that ESRD causes fluid retention, that OSA is very common in ESRD, and that OSA increases cardiovascular risk [2,3,11], it is important to examine potential mechanisms through which fluid retention, nocturnal rostral fluid shift, and OSA may contribute to potentially reversible changes in cardiac structure in ESRD patients.

The left atrium plays a crucial role in maintaining optimal cardiac function. It modulates left ventricular (LV) filling by acting as a reservoir during ventricular systole, a conduit during early diastole, and as an active pump in late diastole [12]. Its thin-walled structure means that it is more distensible than the left ventricle in response to increases in pressure or volume of pulmonary venous inflow [13]. The most common causes of an enlarged left atrium are LV dysfunction or hypertrophy, mitral valve disease, and fluid overload [13,14]. The relationship with fluid overload is of particular relevance in ESRD, given that fluid overload is a hallmark of this condition and predicts increased mortality [15].

The high prevalence of OSA in ESRD and in heart failure [16], both pathological states characterized by fluid overload, has led to an interest in the role of fluid retention and fluid shift from the legs in the pathogenesis of OSA in these conditions. In ESRD, the increased prevalence of OSA is not explained solely by comorbidities or increased body mass index (BMI) [17]. Indeed, OSA patients with ESRD tend to have a lower mean BMI than OSA patients with normal

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renal function [2,17,18]. The severity of OSA has been shown to be directly related to the degree of overnight rostral fluid shift from the legs in both heart failure [19] and ESRD patients [10]. In ESRD patients, the volume of fluid accumulating in the legs during the day is likely to be greater than in the general population. Consequently, it is likely that fluid overload and increased overnight fluid shift from the legs play important roles in the pathogenesis of OSA in this population. As fluid overload and rostral fluid shift might distend the LA and increase fluid accumulation in the neck, we postulated that in ESRD patients, LA size would be related to the degree of overnight rostral fluid shift and that, in turn, OSA severity would be related to LA size. To test this hypothesis, we examined LA size determined by echocardiography in relation to OSA severity as determined by polysomnography (PSG) in patients with ESRD.

2. Methods

2.1. Subjects

Inclusion criteria were patients with ESRD at least 18 years of age undergoing thrice-weekly hemodialysis at the University Health Network Toronto General Hospital. Patients were recruited consecutively irrespective of symptoms of sleep apnea. Exclusion criteria were patients who were already treated for OSA or had an LV ejection fraction (LVEF) of <45%.

2.2. Protocol

2.2.1. Echocardiography

As part of routine clinical care in the hemodialysis unit, all patients with ESRD undergo echocardiography yearly. Transthoracic echocardiography was performed using a sector array between 1 and 5 Hz. Two-dimensional echocardiographic images were acquired from the parasternal long and short axes, apical long axis, apical four-chamber, apical two-chamber, and subcostal views.

Variables recorded were LVEF, LV mass, and LA size. LVEF was measured using the biplane Simpson's method using the apical four-chamber and apical two-chamber views. LA size was estimated by measuring the maximum internal anteroposterior diameter of the LA, using the parasternal long axis view. *LV mass was estimated using the American Society of Echocardiography (ASE)-recommended formula:* $LV\ mass = 0.8 \times (1.04\,(LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3) + 0.6\ g$, *where LVIDD is the LV internal diameter in diastole, PWTD is the posterior wall thickness in diastole, and IVSTD is the interventricular septum thickness in diastole. LA size index and LV mass index were calculated by expressing LA size and LV mass, respectively, per unit body surface area.*

All echocardiograms were performed and reported prior to PSG so that the sonographer and reporting cardiologist were unaware of the patient's PSG findings and whether or not they had OSA.

2.2.2. Polysomnography

All subjects underwent overnight PSG the day before dialysis. Prior to PSG, demographic characteristics, medical history, and prescribed medications were recorded. PSG was performed with the use of standard techniques and scoring criteria for sleep stages and arousals from sleep [20]. All subjects slept on a single pillow with the bed flat. Thoracoabdominal motion was monitored by respiratory inductance plethysmography, and nasal airflow was monitored by nasal pressure cannulae (Binaps model 5500; Salter Labs, Arvin, CA, USA). Arterial oxyhemoglobin saturation (SaO_2) was monitored by oximetry. Obstructive apnea was defined as a >90% reduction of tidal volume for ≥10 s with thoracoabdominal motion, and obstructive hypopnea was defined as a 50–90% reduction in tidal volume from baseline for ≥10 s with out-of-phase thoracoabdominal motion or airflow limitation on nasal pressure. Apneas were classified as central in the absence of thoracoabdominal motion, and hypopneas were classified as central in the presence of in-phase thoracoabdominal motion and without airflow limitation on nasal pressure. Although these methods for classifying hypopneas as obstructive or central are in keeping with the criteria recommended by the American Academy of Sleep Medicine (AASM) for scoring hypopneas [21] and in most instances the distinction is clear, in others it is not. Thus, these techniques provide a reasonable approximation of the numbers of obstructive and central hypopneas. The apnea–hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of sleep. Signals were recorded on a computerized sleep recording system (Sandman; Nellcor Puritan Bennett Ltd, Ottawa, Canada) and scored by personnel blind to measurements of leg fluid volume (LFV), neck circumference (NC), and echocardiographic findings.

2.2.3. LFV And neck circumference

A subset of patients agreed to have assessments of LFV and NC. With subjects instrumented for PSG, lying awake and supine with the legs straight, LFV was assessed by measuring the impedance to electrical flow between the electrodes placed on the ankle and upper thigh of the right leg by a bioelectrical impedance device (Xitron Hydra, model 4200, Xitron Technologies Inc., San Diego, CA, USA), as previously described [19,22–24]. This well-validated technique [25,26] uses the impedance to electric current within a body segment to measure its fluid content. Alterations in the fluid content of tissues cause proportional changes in impedance. NC was measured at the superior border of the cricothyroid cartilage with a tape measure. Lines drawn at this level ensured that measurements before and after sleep were made at the same place. On awakening the next morning, measurements made before sleep were repeated. The differences between LFV and NC, before and after sleep, were considered as the overnight changes in LFV (ΔLFV) and NC (ΔNC). Measurements of LFV and NC were made prior to scoring of the PSG by personnel unaware of the AHI.

The protocol was approved by the Research Ethics Board of the University Health Network and Toronto Rehabilitation Institute, and all subjects provided written informed consent before participation.

2.3. Statistical analysis

Relationships between single variables were examined by the Pearson correlation coefficient. Multivariable analysis was also undertaken with AHI as the dependent variable and with age, BMI, presence or absence of hypertension, LV mass, and LA size index as the independent variables using multiple stepwise linear regression with $p < 0.05$ to enter and $p > 0.1$ to remove. A similar multivariable analysis was undertaken with LA size index as the dependent variable and with ΔLFV, age, BMI, and presence or absence of hypertension as the independent variables. Data are presented as mean ± standard deviation (SD) unless indicated otherwise. A p value <0.05 was considered significant. Analyses were performed with the use of SPSS 21.0.1 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Characteristics of the patients

Forty ERSD patients underwent PSG and an echocardiogram was performed. Their characteristics are shown in Table 1. The study population was receiving adequate dialysis, as indicated by a percent reduction of urea >65% in all. The great majority of apneas and hypopneas were obstructive. A subset of the last 21 patients underwent LFV assessment.

Table 1
Characteristics of the patients who underwent polysomnography and echocardiography.

	$n = 40$
Men : Women	22:18
Age	47.1 ± 15.9
BMI, kg/m^2	27.5 ± 6.7
Reduction of urea, %	76.1 ± 10.2
AHI, events/h of sleep	25.1 ± 23.4
Obstructive AHI	21.7 ± 21.0
Central AHI	2.5 ± 4.6
LVEF%	64.4 ± 7.1
LV mass, g	204.1 ± 85.6
Left atrial size, mm	39.7 ± 7.8
Left atrial size index, mm/m^2	22.0 ± 4.9
Hypertension (n)	24
Atrial fibrillation (n)	1
Diabetes (n)	13

Abbreviations: BMI = body mass index, AHI = apnea–hypopnea index, LVEF = left ventricular ejection fraction.
Data are presented as mean ± standard deviation unless otherwise indicated.

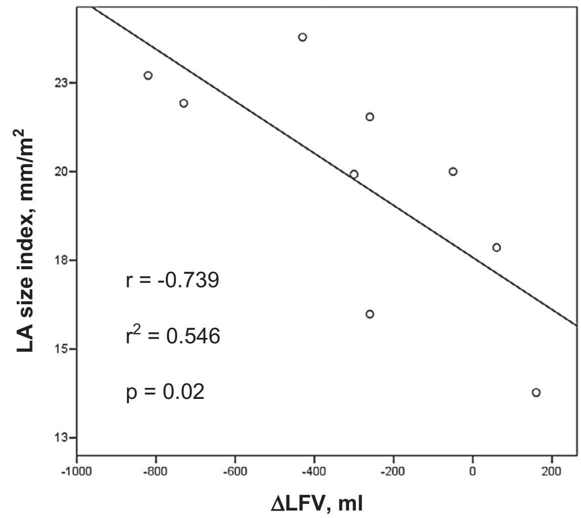

Fig. 2. Relationship between left atrial (LA) size index and overnight change in leg fluid volume (ΔLFV) in men.

3.2. Polysomnographic and echocardiographic data

Among the 40 patients, there was a significant correlation between AHI and LA size ($r = 0.626$, $p < 0.001$). In men, this relationship persisted ($r = 0.617$, $p = 0.002$) and became even stronger when LA size was indexed to body surface area ($r = 0.743$, $p < 0.001$, Fig. 1). In women, there was no significant relationship between AHI and LA size ($r = 0.434$, $p = 0.07$) or AHI and LA size index ($r = 0.325$, $p = 0.30$). In men, there was also a significant relationship between LV mass index and AHI ($r = 0.697$, $p = 0.001$) that was not seen in women ($r = 0.219$, $p = 0.38$). Stepwise multiple regression analysis in men revealed that the only factor that correlated independently with the AHI was the LA size index ($r = 0.781$, $r^2 = 0.609$, $p < 0.001$).

3.3. LFV measurements

Twenty-one patients underwent LFV assessments in addition to PSG and echocardiography. There were nine men and 12 women whose age was 43.8 ± 14.6 years, BMI was 27.1 ± 7.3 kg/m^2, and AHI was 18.3 ± 21.8 events/h of sleep. Among the men, there was a strong inverse correlation between LA size index and Δ LFV ($r = -0.739$, $p = 0.02$, Fig. 2) and also between AHI and Δ LFV ($r = -0.863$, $p = 0.003$, Fig. 3). Stepwise multiple regression analysis, in men, revealed that the only factor that correlated independently with the LA size index was Δ LFV ($r = -0.739$, $r^2 = 0.546$, $p = 0.02$). In women, there was a significant relationship between LA size and ΔLFV ($r = 0.601$, $p = 0.04$), but no relationship between LA size index and ΔLFV ($r = 0.077$, $p = 0.81$). There was also no relationship between AHI and ΔLFV in women ($r = 0.028$, $p = 0.93$). In addition, in men, there were significant relationships between AHI and LA size ($r = 0.719$, $p = 0.03$) and between AHI and LA size index ($r = 0.833$, $p = 0.005$). However, in women, these relationships were not significant ($r = 0.389$, $p = 0.21$ and $r = 0.325$, $p = 0.3$, respectively). There was no relationship between ΔLFV and LV mass index in men or women. In men, there was a direct relationship between ΔNC and LA size index ($r = 0.703$, $p = 0.04$) that was not seen in women ($r = 0.065$, $p = 0.84$).

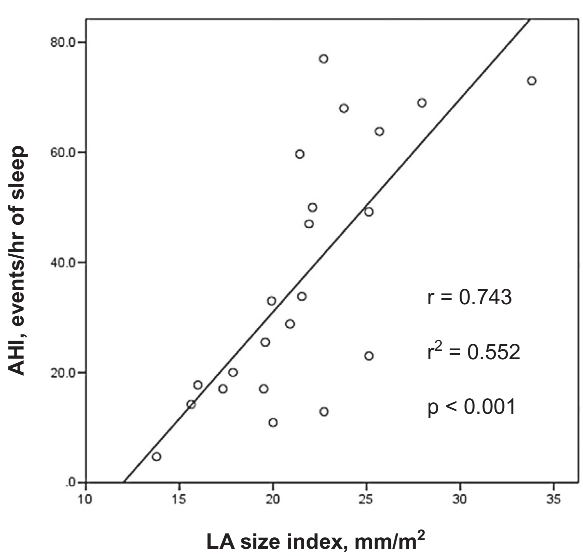

Fig. 1. Relationship between apnea–hypopnea index (AHI) and left atrial (LA) size index in men.

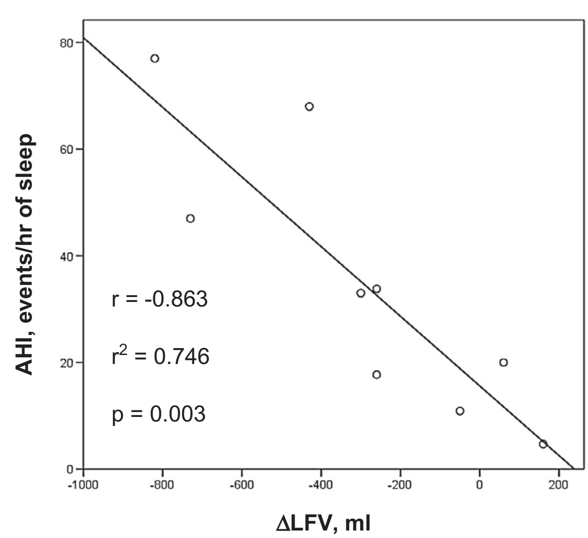

Fig. 3. Relationship between apnea–hypopnea index (AHI) and change in overnight leg fluid volume (ΔLFV) in men.

4. Discussion

This study provides novel insights into potential mechanisms linking fluid retention and overnight rostral fluid shift with cardiac structure and OSA severity in ESRD patients on conventional hemodialysis. We found, in men, that there was a strong, direct relationship between severity of OSA, assessed by the AHI, and LA size. We also showed in men that there were strong relationships between the Δ LFV and both the LA size and the severity of OSA. Furthermore, in men, there was a relationship between the overnight change in NC and LA size. In women, however, there were no significant relationships between LA size and OSA severity, NC, or ΔLFV.

Fluid retention in ESRD is a major therapeutic challenge as it can lead to leg edema, pulmonary congestion, and systemic hypertension [27–29]. It is also associated with increased cardiovascular mortality, such that higher inter-dialytic weight gain is associated with increased cardiovascular deaths and worse survival [15]. However, the mechanisms by which fluid retention contributes to increased mortality have not been elucidated. Our study suggests that ΔLFV, LA size, and OSA severity may be involved in this relationship. In ESRD patients, it is possible that not only could fluid moving out of the legs overnight shift rostrally into the neck but it could also redistribute to the thorax and heart where it may distend the LA. This may, in turn, lead to an increase in central venous pressure, further fluid accumulation in the neck, an increase in pharyngeal collapsibility, and an increase in OSA severity. The observation that increased fluid removal via nocturnal peritoneal dialysis versus conventional continuous ambulatory dialysis leads to an increase in pharyngeal size and a reduction in AHI is in keeping with this proposal [30]. This possibility is further supported by our finding in this study of a strong relationship between LA size and ΔNC.

Increased LA size predicts increased cardiovascular mortality in ESRD patients, independently of LV mass or systolic dysfunction [5,31]. The LA can enlarge secondary to other cardiac pathology such as LV dysfunction, LV hypertrophy, or mitral valve disease [13,14]. However, its thin-walled structure makes it very susceptible to distension from pressure and volume overload, even in the absence of other cardiac pathology [13]. In this study, patients were excluded if their LVEF was <45% and their mean LVEF of 64 % is well within normal limits indicating normal systolic function. In addition, no patient had significant mitral or other valvular heart disease. There was a relationship between LA size and LV mass. However, while LA size index correlated strongly with ΔLFV, LV mass and LV mass index did not. The strong relationships seen between LA size and ΔLFV and between the AHI and LA size suggest that increased mortality associated with LA size may be at least partly related to the degree of overnight fluid shift from the legs and to the presence and severity of OSA.

It is also possible that diastolic dysfunction, which is common in patients with ESRD [32], contributed to the relationships among fluid overload, overnight fluid shift, LA size, and sleep apnea severity. However, diastolic dysfunction, itself, is profoundly influenced by alterations in preload and as this is constantly changing in ESRD because of pronounced fluid volume shifts from day to day due to dialysis, it is very difficult to reliably diagnose diastolic dysfunction in ESRD patients by echocardiography alone. Furthermore, in the setting of preserved LV systolic function, recent guidelines advise that flow Doppler measurements alone are not adequate to identify diastolic dysfunction and recommend the use of tissue Doppler at the very least [33]. However, tissue Doppler was not performed in this study. In any case, given the limitations of echocardiography in distinguishing true diastolic dysfunction from volume overload, it is likely that more invasive investigations would be required to make a definitive diagnosis of diastolic dysfunction in ESRD patients such as ours.

OSA is much more common in men than women in the general population as well as in ESRD patients [8,34]. Various factors, such as a shorter pharynx, different neck fat distribution, genioglossus activity, and hormonal status, may reduce women's susceptibility to OSA [35–37]. None, however, can fully explain the difference in OSA prevalence between men and women [37]. While we found a direct relationship between ΔLFV and AHI in men, we found no such relationship in women, consistent with our previous findings in patients with heart failure [38]. Previous studies have also shown that for a similar degree of fluid shift from the legs, the increase in NC and UA collapsibility was much greater in men than in women [19,39]. In women, a greater proportion of the fluid shifting from the legs may be redistributed to areas aside from the neck such as the large venous plexi around the uterus and ovaries. It is therefore possible that differences in the pattern of overnight fluid redistribution might be another factor that contributes to the lower prevalence of OSA in women than in men.

In summary, we report novel data demonstrating that LA size is related to both ΔLFV and severity of OSA in men but not in women with ESRD. Thus, in men, the relationship between LA size and mortality in ESRD may also be linked to degrees of fluid overload, overnight rostral fluid shift, and severity of OSA. Further studies of overnight fluid redistribution that include measurements of fluid volumes of the abdomen, thorax, and neck may help determine if the difference in OSA prevalence between men and women can be explained by sex-specific differences in fluid redistribution patterns. Finally, given the relationships among overnight fluid shift from the legs and both LA size and OSA severity, and their potential contribution to increased mortality in this high-cardiovascular risk group, our results highlight the importance of determining whether removal of excess fluid by intensified dialysis or ultrafiltration would reduce LA size and OSA severity in ESRD patients.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.07.001.

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